Major depressive disorder (MDD) is the world’s leading cause of disability, affecting 300 million people worldwide. Approximately one third of MDD patients have treatment-resistant depression (TRD), where they fail to respond to multiple first-line antidepressant therapies. Ketamine, a compound with psychoactive side effects, has recently been shown to have rapid and long-lasting antidepressant effects in TRD patients, however the mechanisms and brain circuits that modulate these effects remain unknown. Research from our laboratory demonstrated that ketamine administration had direct effects on neuronal oscillatory rhythms, neurophysiological brain wave patterns critical to neuronal communication, within and between brain regions implicated in MDD. Thus, we posit that elucidating the neural circuitry activated by ketamine, as well as characterizing concurrent oscillatory changes are key to understanding the superior therapeutic efficacy of ketamine. We will be infusing retrograde adeno-associated viral vectors to deliver a DREADD-Gq into multiple regions to tag and stimulate the neural circuitry previously activated by ketamine in a TRD rat model system and to visualize this circuitry in 3-D using iDISCO. Simultaneously, rats will undergo intracranial electrode implantation into these same regions to assess ketamine-induced circuit function changes. We hypothesize that stimulation of the ketamine-activated circuitry will mimic the therapeutic effects of ketamine. This research will provide novel insights into circuit function changes induced by ketamine, thereby providing critical information regarding potential targets of alternative therapies with fewer negative side effects for TRD management.